Appendix E

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PAPER

Weight management using a meal replacement strategy: meta and pooling analysis from six studies

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OBJECTIVE: Although used by millions of overweight and obese consumers, there has not been a systematic assessment on the safety and effectiveness of a meal replacement strategy for weight management. The aim of this study was to review, by use of a meta- and pooling analysis, the existing literature on the safety and effectiveness of a partial meal replacement (PMR) plan using one or two vitamin/mineral fortified meal replacements as well as regular foods for long-term weight management.
DESIGN: A PMR plan was defined as a program that prescribes a low calorie (>800 ≤1600 kcal/day) diet whereby one or two meals are replaced by commercially available, energy-reduced product(s) that are vitamin and mineral fortified, and includes at least one meal of regular foods. Randomized, controlled PMR interventions of at least 3 months duration, with subjects 18 y of age or older and a BMI ≥ 25 kg/m^2, were evaluated. Studies with self-reported weight and height were excluded. Searches in Medline, Embase, and the Cochrane Clinical Trials Register from 1960 to January 2001 and from reference lists identified 30 potential studies for analysis. Of these, six met all of the inclusion criteria and used liquid meal replacement products with the associated plan. Overweight and obese subjects were randomized to the PMR plan or a conventional reduced calorie diet (RCD) plan. The prescribed calorie intake was the same for both groups. Authors of the six publications were contacted and asked to supply primary data for analysis. Primary data from the six studies were used for both meta- and pooling analyses.
RESULTS: Subjects prescribed either the PMR or RCD treatment plans lost significant amounts of weight at both the 3-month and 1-year evaluation time points. All methods of analysis indicated a significantly greater weight loss in subjects receiving the PMR plan compared to the RCD group. Depending on the analysis and follow-up duration, the PMR group lost ~7–8% body weight and the RCD group lost ~3–7% body weight. A random effects meta-analysis estimate indicated a 2.54 kg ($P<0.01$) and 2.43 kg ($P=0.14$) greater weight loss in the PMR group for the 3-month and 1-y periods, respectively. A pooling analysis of completers showed a greater weight loss in the PMR group of 2.54 kg ($P<0.01$) and 2.63 kg ($P<0.01$) during the same time period. Risk factors of disease associated with excess weight improved with weight loss in both groups at the two time points. The degree of improvement was also dependent on baseline risk factor levels. The dropout rate for PMR and RCD groups was equivalent at 3 months and significantly less in the PMR group at 1 y. No reported adverse events were attributable to either weight loss regimen.
CONCLUSION: This first systematic evaluation of randomized controlled trials utilizing PMR plans for weight management suggests that these types of interventions can safely and effectively produce significant sustainable weight loss and improve weight-related risk factors of disease.
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Keywords: obesity; dietary management; weight loss treatment; meta-analysis; pooling analysis

Introduction

Energy reduced diets are the cornerstone of modern weight control efforts.[1–4] Healthcare providers have at least two dietary options when prescribing a weight loss regimen. The first option is as a very low calorie diet (VLCD) that uses calorie controlled, vitamin/mineral fortified liquid meals taken as the sole nutrient source.[5–7] These diets are medically supervised and provide <800 kcal/day. VLCDs are typically prescribed for the morbidly obese or for those in whom rapid weight loss is a medical necessity. Studies indicate that VLCDs are safe when used as recommended.[6–8]

The second option is a low calorie diet (LCD) supplying >800 kcal/day, usually in the range of 1200–1600 kcal/day.

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These are food-based strategies that can be divided into three categories: a traditional reduced calorie diet (RCD) plan that utilizes a food regimen;[3–5] a meal plan of prepackaged foods and snacks that are vitamin/mineral fortified;[9] and a partial meal replacement (PMR) plan that prescribes one or two portioned-controlled, vitamin/mineral fortified meal replacements along with traditional reduced calorie meal(s) and snacks.[10] Each of the LCD strategies is usually designed to lower caloric intake by 500–1000 kcal/day and is administered in association with behavior modification.[1–4] While most programs for weight reduction have demonstrated promising short-term weight loss results, long-term observations of 1 y or greater have shown high rates of recidivism and weight relapse.[4–6]

Although millions of overweight and obese individuals have utilized an LCD plan on a regular basis, PMR plans have not been critically evaluated for safety and efficacy by the scientific community. This gap in the literature is particularly important as PMR plans, marketed now by several manufacturers, are increasingly used as components of large-scale clinical trials and are also included as a therapeutic component in some new pharmacologic agent efficacy studies. Moreover, many new products and related plans are appearing on the market with little substantiation of their tolerance and weight-loss promoting effectiveness. The report 'Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults—the Evidence Report', prepared by the National Institutes of Health,[1] did not mention the use of meal replacement products, including PMR products, as a weight management tool. Recognizing that a large number of health professionals recommend the use of a PMR plan to patients and PMR products are increasingly used in weight loss studies, there is a need for a critical evaluation of available published results.

The aim at the outset of this study was to evaluate the results of all available PMR plans and products. However, an extensive literature search identified only a limited number of randomized controlled trials and all of these trials used the same commercial product (Figure 1). We were therefore only able to carry out a meta-analysis of one PMR plan. As the number of qualified studies identified was recent and limited to six that met predefined criteria, we were able to contact authors and obtain original data from each study for meta-analysis.

Methods

Definitions

Presently, there are no established definitions of 'meal replacement' or PMR plans. The term meal replacement as

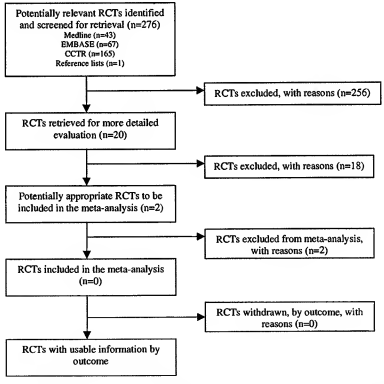

Figure 1 Literature search and selection plan for traditional meta-analysis PMR articles. Abbreviation: CCTR, Cochrane controlled trial register, RCTs, randomized controlled trials.

applied in the scientific literature encompasses a wide range of food products that includes beverages, prepackaged shelf-stable and frozen entrees, and meal/snack bars. These foods can be used as the sole energy source for a meal or in combination with other foods. Meal replacements can be purchased at medically supervised weight loss clinics, commercial weight loss centers, and over the counter. The majority of meal replacement products are vitamin/mineral fortified and designed to replace one or two regular meals or snacks daily and provide for a nutritionally balanced low fat, low energy meal plan. Most commercial programs also advise on the composition of regular meals, between-meal snacks, behavior modification, and physical activity.

The following operational definition of a PMR plan was formulated for evaluation of relevant studies: a PMR plan or program includes one or more meals replaced by a commercially available, calorie-reduced product(s) that are fortified with vitamins and minerals and at least one daily meal consisting of regular foods. As an LCD, the plan's calorie-content should be $>800 \leq 1600$ kcal/day. This definition encompasses several commercially available PMR plans.

Data sources and study selection

This study conducted both a traditional meta-analysis based on published results and a pooled analysis on individual subject data provided by the authors of published studies. All but one of the studies were previously published in peer-reviewed journals.[11–16] The remaining study was presented at a national meeting, published as an abstract, and subsequently submitted for publication.[17]

The studies were identified through searches for clinical trials with meal replacement or meal plans in Medline, Embase, and the Cochrane Clinical Trials Register from 1960 to January 2001. This review was supplemented by a manual search of bibliographies. From a potential list of 276 publications, 30 met the criteria as a meal replacement and 20 were eliminated for reasons listed in the Appendix.[18–34] Of the remaining 10, four were eliminated for lack of a prospective control arm and six met the criteria for analysis: (1) PMR according to the stated definition, (2) randomized trial comparing PMR to a traditional low calorie diet plan, (3) study duration >3 months, (4) subjects >18 y, (5) no self-reported data included. In the fifth study (ULM), the control group followed an RCD for the first 3 months and then the PMR plan for the subsequent 9 months of treatment.[11] Therefore, measurements from these subjects were excluded after completion of the 3-month weight loss phase.

Of the six studies that met all inclusion criteria (ULM, UCLA, MAYO, NEV, TP, SDA),[11–17] five were conducted in the United States and one in Germany (ULM).[11] All six studies had a parallel design in which the control group was

Table 1 Overview of studies included in the individual subject data pooled analysis

	Patient characteristics				
Study (reference)	*N (M/F)*	*Age (y)*	*Baseline BMI (kg/m²)*	*Study duration (months)*	*Treatment*
ULM[11,12]	21/79	18–65	27–37, comorbidities allowed	51	*Intervention:* 1200–1500 kcal/day diet with 2 MR and 2 SR; 1MR after 3 months *Control:* Isoenergetic control diet; no control group after 3 months
SDA[13]	30/71	18–56	25–32, healthy	12	*Intervention:* 1200 kcal/day including 1 or more MR *Control:* Isoenergetic traditional low-fat diet
UCLA[14]	39/29	⩾30	27–40+NIDDM	3	*Intervention:* SF plan with 2 MR with and without added sugar (data combined) *Control:* American Diabetic Association diet
MAYO[15]	13/20	40–65	30–40+NIDDM	12	*Intervention:* 10-day Jump Start, up to 10% wt loss 2 MR, after 10% wt loss 1 MR *Control:* Isoenergetic diabetic diet
NEV[16]	0/75	30–50	25–35+weight gain in previous year, healthy	12	*Intervention:* (1) a traditional lifestyle-group with 2 MR/day; (2) 2MR/day with brief individual visits by physician or office nurse (not included) *Control:* Traditional lifestyle-group
TP[17]	12/83	30–65	25–30, healthy	12	*Intervention:* SF plan with 2MR/day *Control:* 1500 kcal/day control diet

MR, meal replacement; NIDDM, non insulin-dependent diabetes; SF, Slim-Fast; SR, snack replacement; ULM—University of Ulm, Obesity Center; SDA—Study conducted by Dana Rothacker at a CRO. SDA is the other Danny company; UCLA—University of California, Los Angeles - Dave Heber's 12-week diabetes study (OBesity Res supplement); MAYO—Mayo Clinic-Don Hensrud's study (Obesity Research Supplement); University of Nevada, Reno; Travis Pharmacy, Shenondoah Iowa.

prescribed a conventional RCD diet with the same caloric composition as the control group (Table 1). The PMR intervention group replaced two meals per day with liquid MRs during the weight loss phase and one meal per day with a liquid MR in the weight maintenance phase. The SDA-group used one MR per day in place of a meal throughout the 1 y study.[13] The UCLA-group used two meal replacements differing in carbohydrate makeup (ie, one with added sugar and the other without).[14] Primary end points in these two groups did not differ statistically ($P > 0.05$) and the groups were pooled. The NEV-study had two PMR intervention groups, one dietitian-based and the other physician-based.[16] The dietitian-based group had the same treatment as the control group, with the exception of the meal replacement plan, and was selected as the intervention group. Patients enrolled in four of the studies had no co-morbidities whereas the other two studies were designed to manage subjects with type II diabetes.[14,15] All enrolled subjects gave informed consent after Institutional review board approval of the protocols. Within each study, subjects received the same behavioral modification program, dietary instruction regarding caloric intake and exercise prescription.

Quality assessment and data extraction

Study quality was assessed using the Jadad criteria: random allocation of treatments with a clear description of randomization procedure; blinding of the patient for the assigned treatment; blinding of the outcome assessor; and description of dropouts and missing values.[35] Although the criteria assess reporting quality rather than study quality, it has been recognized by the Cochrane Collaboration group and has a sound empirical basis.[36] Quality scores were not used as a threshold for inclusion or exclusion of studies, an approach suggested by several research groups.[37–39]

The quality of all studies as assessed by the Jadad-criteria was moderate. Blinding of the patients was not possible due to the nature of the interventions. Blinding of the outcome assessor was not described in any of the protocols or publications, whereas a description of randomization was apparent in all of the protocols. All of the studies provided descriptions of subjects who dropped out before study completion.

Statistical analysis

Descriptive statistics of variables used in the present study were computed for each group. The significance of between-group differences was evaluated by Student's *t*- and χ^2 tests.

To estimate the effect of the PMR on weight loss, the 3-month and 1-*y* weight losses were calculated as the difference in weight at these two time points from baseline values. The effectiveness of the PMR intervention was measured by the weight loss difference between PMR and control groups (ie, *PMR weight loss–control weight loss*). Similarly, biomarker effects were defined as the changes observed at 3 months and 1 y. The eight biomarkers evaluated were fasting plasma glucose, insulin, cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triacylglycerols (TAG), and systolic and diastolic blood pressure (SBP, DBP).

Meta-analysis. Study estimates of weight loss in both groups and the group effect adjusting for gender, baseline age, and baseline BMI was obtained with a general linear regression model; the variables adjusted for were included as covariates. The estimates from the models for the individual studies were then meta-analyzed with the studies treated as fixed[39] and random[40] effects. Heterogeneity of estimates was followed using a χ^2 test.[41] Assessment of possible publication bias was carried out by calculating "fail-safe-N"[42] and Kendall's tau statistic.[43] Missing imputation was not applied for this meta-analysis.

Pooling analysis. To obtain single estimates for each effect of interest, the primary data from the six studies were pooled into a single data set. The estimates (ie, weight loss in the control group, weight loss in the PMR group, and between-group weight loss) were then obtained after adjusting for gender, baseline age, baseline BMI, study effects, and interaction between study and group effects, where the study effects were treated as random. Estimate heterogeneity was assessed by means of testing the significance of interaction between study and group effects. This pooling analysis was also applied to data with missing imputations such as the last-observation-carried-forward (LOCF) method and a multiple imputation (MI) method.[43]

Since obese subjects with adult onset diabetes mellitus (DM) are felt to be more resistant to weight loss than non-diabetics,[44,45] a stratified analysis by diabetic status using the same modeling procedure was conducted to evaluate the independent contribution of diabetes to weight loss.

Biomarker analysis. A general linear model was applied to the pooled data for each risk factor to evaluate if the risk factor improvements were associated with their respective baseline values, weight loss, and treatment assignment. The models included random study effects as covariates along with baseline risk factor level, weight loss, and treatment effect as independent variables.

Statistical significance was set at the $\alpha = 0.05$ level. All of the analyses presented abided by the 'intent-to-treat' principle and were performed by SPSS v.10.0 (SPSS Inc., 2001) and S-plus 2000 (MathSoft Inc., 1999).

Results

Combining the six data sets produced 249 PMR-treated subjects and 238 control subjects (Table 2). Female subjects comprised 75% of the population with a mean age of 46.1 y and a mean BMI at baseline of 31.0 kg/m^2. There were 119 subjects with DM (UCLA and MAYO study subjects) and 368 non-DM subjects. Baseline glucose was the only risk factor

that differed significantly between the PMR and RCD groups ($P=0.034$).

Weight loss at the 3-month follow-up

The dropout rate was not significantly different between the PMR and RCD treatment groups at 3 months: 16 and 19%, respectively ($P=0.407$). None of those who dropped out reported program or product-related adverse events.

All six individual studies resulted in significant weight loss in both PMR and RCD groups (Table 3). Weight loss was greater in the PMR group with significance between studies ranging from $P<0.001$ to 0.496 (Table 3). Synthesized estimates from both meta- and pooling analysis of the six

Table 2 Descriptive statistics

	RCD			*PMR*			*Total*		
Baseline measurements	N	*Mean*	*s.d.*	N	*Mean*	*s.d.*	N	*Mean*	*s.d.*
Age (y)	238	46.5	11.3	248	45.7	11.3	486	46.1	11.3
Weight (kg)	238	86.8	14.7	248	87.4	14.6	486	87.1	14.7
Height (m)	238	1.67	0.08	249	1.68	0.09	487	1.7	0.09
BMI (kg/m^2)	238	31.1	4.4	248	30.9	3.9	486	31.0	4.2
BF (%)	53	41.0	8.8	48	38.4	9.0	101	39.8	9.0
Glucose (mg/dl)[a]	114	108.7	41.6	146	121.1	50.3	260	115.7	47.0
Insulin (µU/ml)	72	17.6	8.4	75	16.2	7.83	147	16.8	8.13
Cholesterol (mmol/l)	134	5.44	1.03	136	5.48	1.00	270	5.46	1.01
HDL (mmol/l)	134	1.37	0.36	136	1.37	0.38	270	1.37	0.37
LDL (mmol/l)	83	2.95	0.81	85	3.21	0.90	168	3.08	0.86
TAG (mmol/l)	134	1.81	1.11	136	1.77	1.08	270	1.79	1.09
SBP (mmHg)	147	131.1	16.2	156	130.3	17.4	303	130.7	16.8
DBP (mmHg)	110	76.9	10.2	118	77.5	8.2	228	77.2	9.2
Diabetes	238	22%[b]		249	27%		487	24%	
Gender	238	77%[c]		249	73%		487	75%	

[a]Significant differences between Control and PMR groups at 0.05 level. [b]Percentage of diabetics. [c]Percentage of female subjects.
BF, body fat; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TAG, triacylglycerols.

Table 3 Three-month weight loss results

			RCD			*PMR*			*Δ (PMR-RCD)*		
	Study	N	*Wt loss*	*s.e.*	*P-value*	*Wt loss*	*s.e.*	*P-value*	*Wt*	*s.e.*	*P-value*
Individual	ULM	100	1.57	0.48	0.001	7.38	0.46	<0.001	5.81	0.60	<0.001
	UCLA	65	4.05	0.83	<0.001	5.94	0.74	<0.001	1.89	1.11	0.094
	MAYO	30	4.82	1.13	<0.001	6.74	1.03	<0.001	1.92	1.67	0.261
	NEV	50	2.63	0.73	<0.001	5.37	0.59	<0.001	2.75	0.96	0.006
	SDA	91	4.40	0.51	<0.001	6.76	0.53	<0.001	2.37	0.71	0.001
	TP	67	4.41	0.63	<0.001	4.90	0.58	<0.001	0.49	0.71	0.496
Meta	Fixed	403	3.34	0.26	<0.001	6.28	0.24	<0.001	3.01	0.33	<0.001
	Random	403	3.56	0.60	<0.001	6.19	0.44	<0.001	2.60	0.96	0.006
Pooled	Completer	403	3.96	0.29	<0.001	6.50	0.27	<0.001	2.54	0.37	<0.001
	LOCF	485	3.23	0.28	<0.001	5.62	0.26	<0.001	2.39	0.35	<0.001
	MI	487	3.99	0.29	<0.001	6.22	0.27	<0.001	2.23	0.35	<0.001
Q			24.21	5.00	<0.001	15.06	5.00	0.010	37.04	5.00	<0.001
Publication	Fail-safe-N		137			377			60		
Bias	tau		0.07		0.851	−0.200		0.573	−0.200		0.573

Wt loss (kg)=Wt at Baseline-Wt at 3 Mo (adjusted for gender, age, and baseline BMI). The six studies are summarized in Table 2.
LOCF, last observation carried forward; MI, multiple imputation.

studies showed significant weight loss in both groups as well as significantly greater weight loss in the PMR-treated subjects (Table 3). Specifically, based on the fixed-effects meta-analysis, the random effects meta-analysis, and the pooling analysis of the completers, the weight loss estimates from the completers ranged between 3.23 and 3.99 kg in the RCD group and between 6.19 and 6.50 kg in the PMR group; the PMR group weight loss ranged from 2.54 to 3.01 kg greater than the RCD group (Table 3). Overall, weight loss at 3 months in the RCD group approximated 4% and in the PMR group 7%.

Hedges and Olkin's Q statistic showed that the estimates of weight loss and the effectiveness of the PMR program from the individual studies were significantly heterogeneous in the meta-analysis (Table 3): $Q=24.2$, ($P<0.001$) for weight loss in RCD; $Q=15.1$ ($P=0.010$) for weight loss in PMR; and $Q=37.0$ ($P<0.001$) for effectiveness. This significance of heterogeneity in effectiveness estimates was supported in the pooling analysis via testing the significance of interactions between group and study effects ($P<0.001$).

Pooling analysis of the data after missing data imputation by either LOCF or MI produced the same results as the completer analysis (Table 3). Figure 2 (a) and (b) summarize the effect sizes of weight loss and effectiveness of the PMR program, respectively, at the 3-month time point.

Weight loss at the 1-y follow-up

Four studies for the RCD and five for the PMR groups were available for the 1-y follow-up analysis (Table 4). At the 1-y evaluation, 64% subjects in the RCD group dropped out compared to 47% of subjects in the PMR group ($P<0.001$). None of those who dropped out reported program or product-related adverse events.

The significance of weight loss at 1 y for the RCD and PMR groups varied by study with P-values ranging from <0.001 to 0.0227 and from <0.001 to 0.056, respectively. Synthesized estimates from both meta- and pooling analysis showed significant weight losses in both groups. Specifically, based on the fixed-effects meta-analysis, the random effects meta-analysis, and the pooling analysis of completers, the weight loss estimates from the completers ranged between 2.61 and 4.35 kg in the RCD group, and between 6.97 and 7.31 kg in the PMR group. Overall weight loss in the PMR groups was greater than that observed in the RCD groups and the level of significance of these differences varied with analysis method (Table 4): 3.39 kg ($P<0.001$) for fixed-effect meta-analysis; 2.43 kg ($P=0.142$) for random-effect meta-analysis; and 2.63 kg ($P=0.003$) for pooling analysis of completers. Overall, weight loss in the RCD group approximated ~3–7% and in the PMR group ~7–8% at 1 y.

Hedges and Olkin's Q statistic showed that the estimates of weight loss and the effectiveness of the PMR plan from the individual studies were significantly heterogeneous in the meta-analysis (Table 4): $Q=23.9$ ($P<0.001$) for weight loss in RCD; $Q=24.6$ ($P<0.001$) for weight loss in PMR; $Q=13.0$ ($P=0.005$) for effectiveness. This significance of heterogeneity in effectiveness estimates was also supported in the pooling analysis by testing the significance of interaction between group and study effects ($P=0.021$).

While the pooling analysis with the data after LOCF missing imputation produced a significantly greater weight loss in the PMR group (2.86 kg, $P<0.001$), the pooling analysis with data after MI did not (1.62 kg, $P=0.142$). However, both MI methods supported the significance of weight loss at 1 y in both groups. Figure 3 (a) and (b)

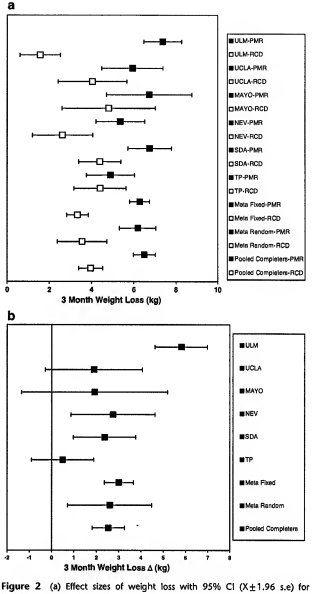

Figure 2 (a) Effect sizes of weight loss with 95% CI ($X\pm1.96$ s.e) for individual PMR studies and all studies combined at 3 months. (b) Weight loss difference (Δ) with 95% CI ($\Delta\pm1.96$ s.e.) between the PMR and RCD programs at 3 months.

Table 4 One-year weight loss results

			RCD			PMR			Δ(PMR-RCD)		
	Study	N	*Wt loss*	*s.e.*	*P-value*	*Wt loss*	*s.e.*	*P-value*	*Wt*	s.e.	*P-value*
Individual	ULM	41	—	—	—	9.79	0.86	<0.001	—	—	—
	UCLA	—	—	—	—	—	—	—	—	—	—
	MAYO	24	1.42	1.18	0.227	2.41	1.26	0.056	0.98	1.86	0.603
	NEV	49	3.50	1.39	0.012	7.57	1.30	<0.001	4.08	1.92	0.039
	SDA	86	1.39	0.71	0.050	6.74	0.73	<0.001	5.35	0.98	<0.001
	TP	19	9.51	1.56	<0.001	8.15	1.14	<0.001	−1.37	1.77	0.452
Meta	Fixed	219	2.61	0.52	<0.001	7.31	0.44	<0.001	3.39	0.72	<0.001
	Random	219	3.77	1.63	0.021	7.01	1.13	<0.001	2.43	1.65	0.142
Pooled	Completer	219	4.35	0.76	<0.001	6.97	0.58	<0.001	2.63	0.88	0.003
	LOCF	485	2.89	0.36	<0.001	5.74	0.33	<0.001	2.86	0.46	<0.001
	MI	487	5.72	0.69	<0.001	7.34	0.69	<0.001	1.62	0.98	0.119
Q			23.90	3.00	<0.001	24.64	4.00	<0.001	13.05	3.00	0.005
Publication	Fail-safe-N		24			166			14		
Bias	tau		1.00		0.042	−0.20		0.624	0.00		1.000

Wt loss (kg)=wt at Baseline–wt at 1 y (Adjusted for gender, age, and baseline BMI). The six studies are summarized in Table 2.
LOCF, last observation carried forward; MI, multiple imputation.

summarizes the effect sizes of weight loss and effectiveness of the PMR program, respectively, at the 1-y time point.

Percentage of subjects losing ≥5% of weight

At 3 months of treatment, 34 and 72% of RCD and PMR groups lost ≥5% of initial body weight, respectively ($P<0.001$). A similar distribution of weight loss and between-group difference (33% *vs* 74%, $P<0.001$) was observed at the 1-y evaluation time point.

Biomarker analyses

The changes in disease risk factors at 3 months are shown in Table 5. After adjusting for random study effects, all of the risk factors improved and were positively associated with their respective baseline values (all $P<0.001$). Improvements in three of the risk factors were significantly positively associated with weight loss during the 3-month treatment period [glucose ($P=0.028$), triglyceride ($P=0.014$), and systolic blood pressure ($P<0.001$)]. There was no significant additional effect of PMR on improvements in the risk factors with the exception of plasma insulin levels ($P<0.001$; Table 5).

The pattern of biomarker improvement was similar at the 1-y evaluation (Table 5). Total cholesterol and LDL-cholesterol were significantly positively associated with weight loss at 1 y in addition to those biomarkers cited at 3 months, glucose ($P=0.009$), LDL-cholesterol ($P=0.001$), triglyceride ($P=0.011$), and systolic blood pressure (<0.001)].

Publication bias

Kendall's tau correlation[46] did not support publication bias, except for the case of weight loss at 1 y in the RCD group, where the correlation is 1 with a *P*-value of 0.042 (Table 4). The sizes of "fail-safe-N" are large at 3-months (60–377), but those for 1 y are relatively small for weight loss in the RCD group, 24, and for the effectiveness of the PMR group, 14.

Pooling analysis stratified by diabetic status

The results of the pooling analysis stratified for diabetic status are presented in Table 6. Separating diabetics and nondiabetics at the 1-y evaluation time point, 60% of non diabetic RCD-treated subjects dropped out compared to 35% of non diabetic PMR-treated subjects ($P<0.001$). In contrast, the dropout rate of diabetics at 1 y was not significantly different between the two treatment groups (77 *vs* 79%, $P=0.78$). This observation implies that both treatments were equally tolerated by diabetics, but that overall recidivism was high. Although the multiple imputation result of PMR effectiveness at 1 y is different from that of the "completers" analysis, it cannot be established if the differing results can be explained by preferential loss of subjects with minimal weight loss.

Regardless of follow-up length, the non-DM subjects remaining in the study lost a significant amount of weight in both groups with significantly greater weight loss in the PMR-treated subjects. The between-group difference was not significant for DM subjects regardless of follow-up length even though PMR-treated diabetic subjects lost a significant amount of weight. The RCD-treated DM subjects also lost a significant amount of weight at 3 months but not at 1 y.

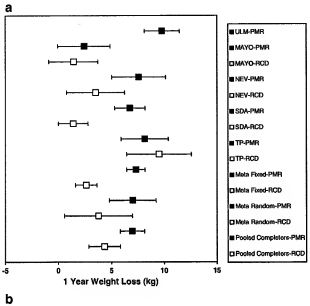

Figure 3 (a) Effect sizes of weight loss with 95% CI (X±1.96 s.e.) for individual PMR studies and all studies combined at 1 y. (b) Weight loss difference (Δ) with 95% CI (Δ±1.96 s.e.) between the PMR and RCD programs at 1 y.

Whichever data were pooled, the weight loss of DM subjects was larger at 3 months than at 1 y. The lower weight loss at one year was not present in the non-DM subjects (Table 6).

Post study PMR reports

Over the course of data analysis and manuscript preparation, two additional recent reports meeting PMR criteria came to our attention.[47,48] The results of both reports are qualitatively consistent with the meta-analytic results developed in the above formal data analysis. Allison *et al*[47] evaluated the safety and efficacy of a low-calorie soy-based PMR program for the treatment of obesity in a 12-week prospective controlled trial. Subjects were randomized to either the 1200 kcal/day PMR program that included liquid shakes or a 1200 kcal/day exchange system diet. Both groups had a single counseling session and were provided with an educational pamphlet at the initial treatment visit. The PMR group lost significantly more weight, by intent to treat analysis, than the control group (7.0 vs 2.9 kg, $P<0.001$) and also had significant biomarker improvements. Cho *et al*[48] randomized subjects to two 12-week dietary intervention programs at a worksite. The subjects were prescribed either a 1200 kcal/day PMR which consisted of breakfast cereal, one meal replacement shake, a cereal bar as a snack, and a sensible dinner or an isocaloric control diet. Mean weight loss from baseline was 7.3 and 6.1 kg for the PMR and control groups ($P<0.07$), respectively.

Discussion

Partial meal replacement efficacy

Although used by millions of overweight and obese consumers worldwide, commercial PMR plans have rarely been the subject of systematic studies using appropriately designed clinical trials.[10] Our subjective impression of this void was confirmed from the literature reviews in the present investigation. Applying reasonable definitions and criteria for randomized PMR trials, an exhaustive literature search failed to disclose any appropriate earlier studies for meta-analysis inclusion other than the six reports for which we were able to acquire the original data. These relatively recent prospective randomized trials were all carried out using contemporary study design concepts and methods.[46] Moreover, the increasing interest in this topic is highlighted by two additional study reports meeting PMR criteria[47,48] that appeared during preparation of this manuscript.

The six evaluated reports individually revealed PMR weight loss efficacy equivalent to or significantly greater than that of RCD treatment. When pooled, weight loss in PMR-treated subjects at 3 months exceeded that of RCD-treated subjects by 2.54–3.01 kg for a total weight lowering of ~7% from baseline. Moreover, at the 1 y time point PMR-related weight loss and maintenance continued to exceed that of RCD by 2.43–3.39 kg for a total reduction from baseline of ~7–8%. Thus, within the context of clinical trials, a PMR plan appears to promote significantly greater weight loss and maintenance than a corresponding RCD plan. The overall magnitude of weight loss in the pooled PMR group at 1 y is in the range often observed in pharmacologic weight control studies[49] and is at the level known to lower disease risk.[1,50,51]

About one-fifth of the study population at baseline was diabetic and consisted of patients from two of the six sites. Although there was no difference in weight loss between diabetic and nondiabetic subjects at 3 months, diabetic patients as a group did not maintain their weight loss at 1 y to the same extent as nondiabetic subjects. Moreover, the recidivism at 1 y in diabetic patients was higher than nondiabetic subjects with both dietary treatments, approaching 80%. Earlier weight loss studies of diabetic

Table 5 Biomarker results

		Independent variables								
		Baseline biomarker			3 month Wt loss			Group (PMR-RCD)		
Dependent variables Δ at 3 Manth	N	Beta	s.e.	P-value	Beta	s.e.	P-value	Beta	s.e.	P-value
Glucose (mg/dl)	177	0.395	0.058	<0.001	1.177	0.530	0.028	7.898	4.522	0.083
SBP (mmHg)	197	0.395	0.057	<0.001	0.957	0.247	<0.001	0.085	1.838	0.963
DBP (mmHg)	197	0.615	0.057	<0.001	0.050	0.129	0.697	−0.143	0.960	0.882
Insulin (μU/ml)	94	0.470	0.089	<0.001	0.117	0.202	0.578	6.603	1.635	<0.001
Cholesterol (mmol/l)	159	0.341	0.051	<0.001	0.030	0.017	0.072	−0.125	0.121	0.302
HDL (mmol/l)	159	0.269	0.061	<0.001	0.007	0.007	0.271	−0.054	0.048	0.261
LDL (mmol/l)	58	0.431	0.088	<0.001	0.060	0.028	0.039	0.037	0.157	0.817
TG (mmol/l)	159	0.281	0.059	<0.001	0.051	0.021	0.014	0.123	0.153	0.424
Δ at 1 y					1 y wt loss					
Glucose (mg/dl)	107	0.617	0.079	<0.001	0.725	0.273	0.009	−2.278	3.895	0.560
SBP (mmHg)	133	0.426	0.072	<0.001	0.733	0.204	<0.001	−1.992	2.665	0.456
DBP (mmHg)	84	0.692	0.106	<0.001	0.154	1.004	0.319	0.344	1.946	0.861
Insulin (μU/ml)	86	0.629	0.088	<0.001	0.151	0.118	0.202	4.027	1.929	0.040
Cholesterol (mmol/l)	103	0.566	0.068	<0.001	0.047	0.011	<0.001	−0.185	0.158	0.245
HDL (mmol/l)	103	0.484	0.069	<0.001	0.002	0.004	0.563	0.048	0.062	0.443
LDL (mmol/l)	64	0.382	0.093	<0.001	0.044	0.012	0.001	−0.161	0.151	0.291
TG (mmol/l)	103	0.806	0.055	<0.001	0.023	0.009	0.011	−0.230	0.127	0.074

Values are adjusted for study.
DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride.
Values are adjusted for age, sex, and study.

Table 6 Pooling analysis of weight loss stratified by diabetic status

				RCD			PMR			Δ (PMR-RCD)		
Subjects	Follow-up period	Pooled data	N	Wt loss	s.e.	P-value	Wt loss	s.e.	P-value	Wt	s.e.	P-value
Non diabetics	3 months	Completers	305	3.49	0.32	<0.001	6.28	0.30	<0.001	2.79	0.37	<0.001
		LOCF	367	2.72	0.30	<0.001	5.39	0.29	<0.001	2.67	0.35	<0.001
		MI	368	3.62	0.28	<0.001	6.10	0.27	<0.001	2.47	0.33	<0.001
	1 y	Completers	193	5.12	0.91	<0.001	8.29	0.61	<0.001	3.17	0.99	0.002
		LOCF	367	2.83	0.44	<0.001	6.40	0.42	<0.001	3.56	0.50	<0.001
		MI	368	4.85	0.61	<0.001	7.77	0.52	<0.001	2.92	0.66	<0.001
Diabetics	3 months	Completers	98	4.88	1.50	0.001	7.34	1.91	<0.001	2.46	1.84	0.185
		LOCF	118	4.36	1.54	0.005	6.98	1.12	<0.001	2.62	1.89	0.167
		MI	119	5.66	1.42	<0.001	7.33	1.05	<0.001	1.67	1.73	0.335
	1 y	Completers	26	1.74	1.16	0.134	4.50	1.53	0.003	2.76	2.00	0.183
		LOCF	118	3.93	1.55	0.011	5.45	1.12	<0.001	1.52	1.89	0.424
		MI	119	1.92	2.07	0.355	4.78	1.43	0.001	2.86	2.53	0.260

LOCF, last observation carried forward; MI, multiple imputation.

patients also indicate a reduced long-term weight loss compared to nondiabetic patients.[44,52]. Less than expected weight loss in patients with diabetes is related to the duration of disease and the need for insulin therapy.[52,53] No adverse events related to glucose control, including hypoglycemia, were reported in any of the reviewed studies and specific weight control investigations of PMR-treated adult onset diabetic patients reported improvements in HbA1c levels as well as a reduction in hypoglycemic medications.[14] Although these observations raise concern for pooling diabetic and non diabetic subjects in efficacy-oriented weight loss trials, PMR efficacy was still maintained at 3 months and 1 y in the sample of 368 nondiabetic patients.

The important question arises as to why PMR treatment improves weight control efforts. First, a growing body of literature supports the effectiveness of structured weight loss plans.[3–5] Wing and Jeffrey found that food provision

increased initial weight loss by 31%[3] and structured meal plans by 61%[4] in obese subjects. These authors suggested that subjects using these strategies had improved behavioral compliance, increased nutritional knowledge, had more regular meals and snacked less.[5] PMRs redirect meal/food selections, potentially replacing self-selected calorie dense foods with a well-defined reduced calorie alternative of known nutritional value. VLCDs replace all meals and represent an extreme in structured diets for weight contro.[3,7,54] Weight loss is substantial in the early phase of VLCD treatment[53,56] and the stress of *ad libitum* food selection is lowered in many subjects during the regular food abstinence period. PMRs may function in a similar way while additionally permitting subjects to develop learning skills in portion sizes as well as maintain an acceptable lifestyle. In addition, the PMR provides a less costly, convenient, and palatable alternative to VLCDs as well as prepared foods. The higher calorie level of PMRs and slower rate of weight loss compared to VLCDs is less likely to promote complications such as cholecystitis. This is consistent with the lack of adverse events were reported in any study patients, including PMR-treated diabetics.

The substantial heterogeneity does not indicate similar effects across all of the studies. The sources of such heterogeneity in this meta-analysis likely include within-center characteristics such as smoking status, alcohol drinking, and physical activity levels that might moderate treatment-related weight loss effects. Nevertheless, the effects of PMR on weight loss are clearly significant from the pooling analysis as well as from individual studies, although the effect size varied over the studies.

Biomarker response

From the medical perspective, weight loss in the present study was associated with improved biomarkers. Relative improvement overall was associated with baseline biomarker level and magnitude of weight loss, confirming similar observations in earlier studies.[57]

The recently introduced ATP III criteria for metabolic syndrome reveal that a congregation of cardiovascular risk factors (ie, lipid, glucose, blood pressure, and waist circumference) is present in 22% of US adults, most of whom are overweight or obese.[58] According to the ATP III report, weight loss, and increased physical activity form the basis for treatment of metabolic syndrome.[59] The good long-term compliance, weight loss, and biomarker improvement in PMR-treated patients suggests that when incorporated into a lifestyle management plan, meal replacements can have a substantial role in management of metabolic syndrome.

Conclusion

Although now used by consumers worldwide for weight control and incorporated as a therapeutic agent in many clinical trials, the effectiveness of PMRs within experimental treatment programs has never been the subject of a systematic review. Moreover, the lack of available information on the topic necessitated our developing a working definition of PMR program and associated controlled trials. Despite only a few trials with published and original data that met these criteria, our results show a clear pattern with equivalent or greater weight loss efficacy of a PMR plan compared to RCD-treatment in individual studies. The collective analysis of six trials showed greater PMR efficacy with biomarker improvement a function of baseline level and weight loss magnitude. Our findings demonstrate the important potential of well-developed PMR products and plans as a means of weight control. This investigation also provides guidance for and can serve as a basis for use of PMR in future weight management programs.

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Appendix

Studies excluded from the traditional meta-analysis with the reason for exclusion are summarized in Table 7.

Table 7

Reference	*Type of intervention*	*Reason for exclusion*
Wadden and Frey[18]	VLCD (OPTIFAST) combined with LCD and conventional diet	Retrospective Self-reported weight and height Type of intervention No control group
Pi-Sunyer *et al*[19]	Prepared meal plan with conventional food (CCNW) as compared to self-selected meal exchange list	10-week study duration Type of intervention No conventional diet as control
Hayes *et al*[9] Hatton *et al*[20] McCarron *et al*[21]	Prepared meal plan with conventional foods (CCNW) as compared to a conventional diet or self-selected diet	10-week study duration Type of intervention
Iselin *et al*[22]	Protein-sparing modified fast with traditional foods (550–750 kcal/day) as compared to conventional diet	Type of intervention Includes subjects <18 y
Summerbell *et al*[23]	Diet consisting of milk only or milk plus one designated food—not supplemented—as compared to a conventional diet	Type of intervention Includes subjects <18 y
Wing and Jeffery[5]	Meal plan with conventional foods with and without food provision as compared to a SBT program	Type of intervention Includes subjects <18 y
Garrow *et al*[24]	VLCD (Cambridge) as compared to milk diet (780 kcal/day) with vitamin/mineral capsule	Type of intervention No conventional diet as control
Wing *et al*[4]	Food provision with conventional foods as compared to no treatment or SBT	Type of intervention No conventional diet as control
Arai *et al*[25]	VLCD supplemented with LCD as compared to LCD and conventional balanced meal	8-week study duration Type of intervention No conventional diet as control

Table 7 (*continued*)

Reference	*Type of intervention*	*Reason for exclusion*
Kirk *et al*[26]	One main meal replaced by cereal serving plus *ad-libitum* high carbohydrate diet during the last 4 weeks	6-week study duration Type of intervention No control group
Metz *et al*[27]	Nutrient-fortified prepared meal plan (CCNW) plus additional low-fat item plus optional daily selection from 'bonus' list, as compared to a self-selected mixed-food plan	10-week study duration Type of intervention No conventional diet as control
Andersen *et al*[28]	PMR as compared to conventional diet	Use of the anorexic drug diethylpropion was allowed
Markovic *et al.*, 1998 (29)	Full MR (Nutri-Metics)	10-week study duration Type of intervention No control group
Pisano *et al*[30]	Conventional diet with 15% of the complex carbohydrates replaced by soluble carbohydrates (Herbalife) (1300–1900 kcal/day) as compared to conventional diet alone	6-week study duration Type of intervention
Rössner and Flaten[31]	Alternation of VLCD and LCD (Nutrilett) with balanced diet with and without solid foods	Type of intervention No conventional diet as control including subjects with treated hypothyroidism
Hey *et al*[32]	Supplemented protein powder as PMR as compared to conventional diet	Use of the anorexic drug diethylpropion was allowed
Anderson *et al*[33]	PMR as compared to full MR (Healthy Management Resources, Boston)	No conventional diet as control
Berra *et al*[34]	Herbalife supplements (fiber, oligoelements, minerals) accompanying a conventional diet as compared to a conventional diet alone	Type of intervention Includes subjects <18 y Includes subjects BMI <25 kg/m^2

CCNW, Campbell's Center for Nutrition and Wellness; LCD, low calorie diet; (P)MR, (partial) meal replacement; SBT, standard behavioral treatment; VLCD, very low calorie diet. More CCNW studies were available, although CCNW are not PMRs and are thus not evaluated further in this table.